Lipids in Health and Disease

REVIEW

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The protective role of brown adipose tissue in cardiac cell damage after myocardial infarction and heart failure

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Abstract

Acute myocardial infarction (AMI) and related cardiovascular disease complications are the leading causes of mortality worldwide. Brown adipose tissue (BAT) is thermogenic and characterized by the uncoupling protein expression. Recent studies have found that in cardiovascular diseases, activated BAT can effectively improve the prognosis of AMI and concurrent heart failure through intercellular communication. However, a clear and systematic understanding of the myocardial protective mechanism of BAT after AMI is lacking, especially in the endocrine function of BAT. This review describes the effects of BAT on various cells in the heart after AMI. BAT plays a protective role on cardiac cells and fibroblasts during ischemia/reperfusion (I/R), myocardial remodeling, and myocardial fibrosis. This review also discusses the changes caused by BAT activation in different stages of heart failure. Finally, this review summarizes the treatment methods that target BAT to improve AMI. Further in-depth researches are still needed to clarify the underlying mechanism of the connection between BAT and different cells in cardiac tissue in order to identify potential therapeutic targets.

Keywords Brown adipose tissue, Acute myocardial infarction, Ischaemia/reperfusion, Myocardial remodeling, Myocardial fibrosis, Heart failure

The human adipose tissues are mainly categorized into thermogenic and non-thermogenic, with the respective representatives being brown adipose tissue (BAT) and white adipose tissue (WAT), BAT is mainly composed of a type of thermogenic adipocyte rich in small lipid droplets and mitochondria. The main feature of BAT are promoting energy metabolism and other cell metabolisms after activation and producing cytokines to regulate target organs through paracrine and endocrine processes. BAT contains various components, including adipose cells, adipose stem cells, endothelial cells, fibroblasts, and lymphocytes. The heat generated by BAT mainly originates from the abundance of mitochondria in brown adipocytes. The inner mitochondrial membrane contains a BAT-specific uncoupling protein 1 (UCP1), forming a proton channel on the inner membrane of the mitochondria. The transfer of H^+ on the cytoplasmic side is mediated by UCP1, which directly transfers H^+ back to the mitochondrial matrix. Therefore, UCP1 induces the uncoupling of oxidative phosphorylation in the mitochondria. The potential energy of the proton concentration gradient difference is directly released in the form of heat energy instead of ATP [1]. The distribution of BAT in the body can be effectively observed through positron emission tomography (PET). Increased uptake of the glucose analogue 18 F-fluorode-

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oxyglucose (18 F-FDG) on computed tomography (CT) images indicates metabolically active BAT [2]. Generally, BAT is mainly distributed in the perirenal and interscapular areas during infancy and gradually decreases with age. However, most adults still have BAT, mainly located between the shoulder blades, neck, supraclavicular region, axilla, paravertebral region and abdomen. In this review, BAT that refers to the classic BAT, which is the remote BAT in the interscapula. Besides its function in energy metabolism, BAT activation linked to multiple cellular metabolic pathways. For example, BAT activation increases systemic glucose metabolism and insulin sensitivity in humans [3, 4]. BAT can also affect the functions of multiple organs and systems through its endocrine effects. Brown adipokines (batokines) encompass both polypeptides and non-peptide molecules, such as lipid molecules and microRNAs [5]. Thermogenic functions, endocrine effects and metabolism effects, of BAT make it crucial for maintaining normal physiological function.

Cardiovascular disease (CVD) is a leading cause of mortality in both China and the United States. Acute myocardial infarction (AMI) and subsequent heart failure (HF) are leading causes of CVD-related mortality [6, 7]. In AMI, the coronary arteries supplying the myocardial cells are occluded, resulting in myocardial ischemia and necrosis, causing cardiac dysfunction and ventricular remodeling. The myocardium is in a pathological state characterized by inflammatory infiltration, local necrosis, fibrosis, and proliferation, with various consequences on the myocardial cells, including compensatory hypertrophy, apoptosis, and necrosis. Currently, percutaneous coronary intervention, together with coronary artery bypass grafting, are the most effective clinical treatment methods for AMI. However, after myocardial cells become ischemic and hypoxic for a period, typical subsequent manifestations include mitochondrial swelling, myofibril relaxation, and glycogen degradation and disappearance, immediately occur. Even after blood flow to the ischemic myocardial tissue is restored, myocardial damage may still be further aggravated, causing secondary damage to the myocardium, known as I/R injury. Moreover, I/R is followed by a chronic process of cardiac cell damage, with ventricular remodeling involving an early inflammatory response, compensatory hypertrophy, metabolic reprogramming of cardiomyocytes, and myocardial fibrosis. These adverse remodeling and pathological conditions increase the risk of HF and death. HF is often a subsequent and concomitant remodeling event following AMI, and its pathogenesis is complex. Overall, AMI and HF were the main causes of CVD-related mortality. Therefore, myocardial protection after AMI and HF is an important research topic.

Recent studies have suggested that BAT activation is related to a reduced risk of cardiovascular events ($p=0.037$) [8]. An F-FDG PET/CT study involving over 50,000 patients with CVD-related diseases, found that BAT activation often predicts a lower risk of cardiovascular diseases and metabolic diseases, such as type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure and hypertension [2]. Cohort studies indicate a negative correlation between BAT activity and arterial inflammation, even after adjusting for age and body mass index, reflecting an increasing BAT uptake rate on PET/CT images [8, 9]. Therefore, activated BAT is thought to exert protective effects against CVDs. Here, the following will review the myocardial protective effect of BAT after AMI and in HF.

BAT communicates with cardiac cells after AMI

After AMI, cardiac muscle cells undergo cell death, accompanied by a decrease in cardiac physiological function. BAT is crucial for protection after AMI. For example, BAT is activated by the pathological processes of I/R after AMI. Increased UCP1 expression was observed in BAT of mice that underwent coronary litigation surgery followed by a 24-h reperfusion, whereas cardiac troponin I (cTnI) levels were higher in UCP 1 knockout mice. In addition, the lower cTnI plasma levels were observed in mice with extra BAT than in controls after AMI. Increased BAT levels in mice correlate with reduced I/R injury after AMI. However, BAT has different myocardial protective effects at different stages after AMI or in subsequent myocardial injury, including I/R, myocardial remodeling, and myocardial fibrosis (Table 1).

BAT and I/R

I/R refers to the phenomenon in which myocardial cells still suffer severe damage even, after blood flow is restored to ischemic myocardial tissues, myocardial cells suffer more severe damage [10]. BAT activation is always after AMI, and the degree is proportional to the left ventricular dysfunction [11]. In UCP1-deficient mice, Akt phosphorylation in cardiac muscle cells decreases, and the underlying myocardial preservation signalling mechanism may be weakened. The PI3K/Akt pathway is implicated in cardiac remodeling, regeneration, and repair following ischemia [12]. Therefore, BAT may play a significant role in myocardial protection during myocardial I/R. Bone morphogenetic protein 3b (BMP3b), a myocardial preservation protein, is secreted by BAT after myocardial ischemia and reperfusion. Plasma levels of BMP3b, a member of the transforming growth factor (TGF) family, positively correlate with AMI size. BMP3b treatment reduces caspase activity in cardiac muscle cells, thereby limiting cardiac muscle cell apoptosis. Mechanistic studies have revealed that after I/R injury, BMP3b may transmit signals through SMAD1/5 phosphorylation and play a role in limiting myocardial

Table 1 Batokines activated in I/R, myocardial remodeling and myocardial fibrosis

Batokines	Class	Model animal	Function	Reference
BMP3B	Protein	Mice with myocardial I/R injury	Reduce I/R injury	[11]
miR-125b-5p miR-128-3p miR-30d-5p	miRNA	Mice receiving MI/R operation	Reduce myocardial ischaemia-reperfusion injury	[14]
Triiodothyronine(T3)	Protein hormone	Mice with left coronary artery was ligated	Regulate biology metabolism	[17]
12, 13 diHOME	Oxylipin	Mice receiving a high-fat diet for 6 weeks and WT mice	Improve cardiomyocyte metabolism	[18]
FGF21	Protein	Mice with hypertension induced by DOCA	Prevent hypertension, cardiac hypertrophy and myocardial fibrosis; reduce the inflammatory damage after myocardial infarction.	[19]
iNOS	Exosomes	Mice with cardiac contractile dysfunction induced by Ang II	Reduce myocardial hypertrophy and the area of myocardial fibrosis	[20]

damage. Animal experiments have revealed that plasma cTnI levels in mice treated with BMP3b are reduced, and that the AMI area is reduced by 35% [11]. Fibroblast growth factor 21 (FGF21), an important cytokine secreted by BAT, plays a protective role against I/R injury. In I/R mice, FGF21 activated NRF2, mediating antioxidant and anti-apoptotic effects in cardiac muscle cells. Activation of the transcription factor NRF2 is crucial in the antioxidative stress response, reducing the AMI area and enhancing cardiac function indicators, such as ejection fraction and end-systolic volume (ESV) [13].

BAT also plays a protective role by secreting small extracellular vesicles (sEVs). The intracardiac injection of BAT-derived sEVs can ameliorate I/R injury. Furthermore, BAT sEVs containing miR-125b-5p, miR-128-3p, and miR-30d-5p (BAT miRNA) are recognized as key myocardial protective factors. BAT miRNAs collectively suppress the pro-apoptotic mitogen-activated protein kinase (MAPK) pathway by targeting molecules like Map3k5, Map2k7, and Map2k4 within the signaling cascade. Other studies have shown that miRNAs play important roles in regulating BAT. For example, Enoxacin can control FGF21 signaling and Ppargc1a expression by regulating miR-34a-5p, thus promoting oxidative metabolism and alleviating obesity. Moreover, FGF21 is an important myocardial protective factor. Therefore, miRNAs can provide myocardial protection through both exosomes acting on cardiomyocytes and adipokines, which directly activate BAT [5]. Therefore, BAT miRNAs and sEVs contribute significantly to myocardial protection [14].

BAT and myocardial remodeling

Cardiac remodeling after AMI involves long-term pathological changes, including early inflammation, compensatory proliferation, and fibrosis. During this period, BAT inhibits adverse myocardial remodeling and improves cardiac function through information exchange with cardiac muscle cells. Previous studies focused on the endocrine functions of BAT in the cardiovascular system. By secreting a variety of batokines [15], BAT participates in regulating various pathways involved in the early inflammatory response, compensatory hypertrophy, and metabolic reprogramming of cardiomyocytes, thereby exerting myocardial protection [16] (Fig. 1). To provide a more comprehensive image of myocardial protective effect of BAT in myocardial remodeling, this section discusses the relationship between myocardial remodeling and BAT in other animal models, such as mice with deoxycorticosterone-induced hypertension, which may be similar to the mechanism of chronic alterations after AMI.

Inflammation occurs first after I/R damage with the myocardial protective effect of batokines activated. FGF21 is an important cytokine of the FGF superfamily. Both activated BAT and highly thermogenic beige adipocytes secrete FGF21, which can reduce inflammation in cardiac muscle cells and limit oxidative stress [19, 21]. In mice, FGF21 knockout significantly increased the protein levels of proinflammatory cytokine genes interleukin (IL)-6 and monocyte chemoattractant protein −1 in the cardiac tissue and plasma. Moreover, FGF21 treatment leads to the inhibition of the NF-kB pathway and a decrease in the transcription of the inflammatory cytokines IL-6 and ANF [22].

In addition to reducing cardiomyocyte inflammation, BAT regulate pathological cardiac hypertrophy. Experiments have shown that the loss of active BAT (iBAT) leads to hypertrophy of mouse cardiac muscle cells, accompanied by the upregulation of the proliferative genes ANP, BNP, and bMHC in neonatal mouse cardiomyocytes (NMCMs) [19]. The batokine FGF21 attenuates phenylephrine-induced cardiomyocyte hypertrophy and induces an increase in PPARγ coactivator-1α (PGC1α) mRNA levels. PGC1α is considered to be closely related to fatty acid oxidation and cardiac hypertrophy [22]. BAT-produced exosomes (BAT-Exos) regulate cardiomyocyte hypertrophy. A previous study found

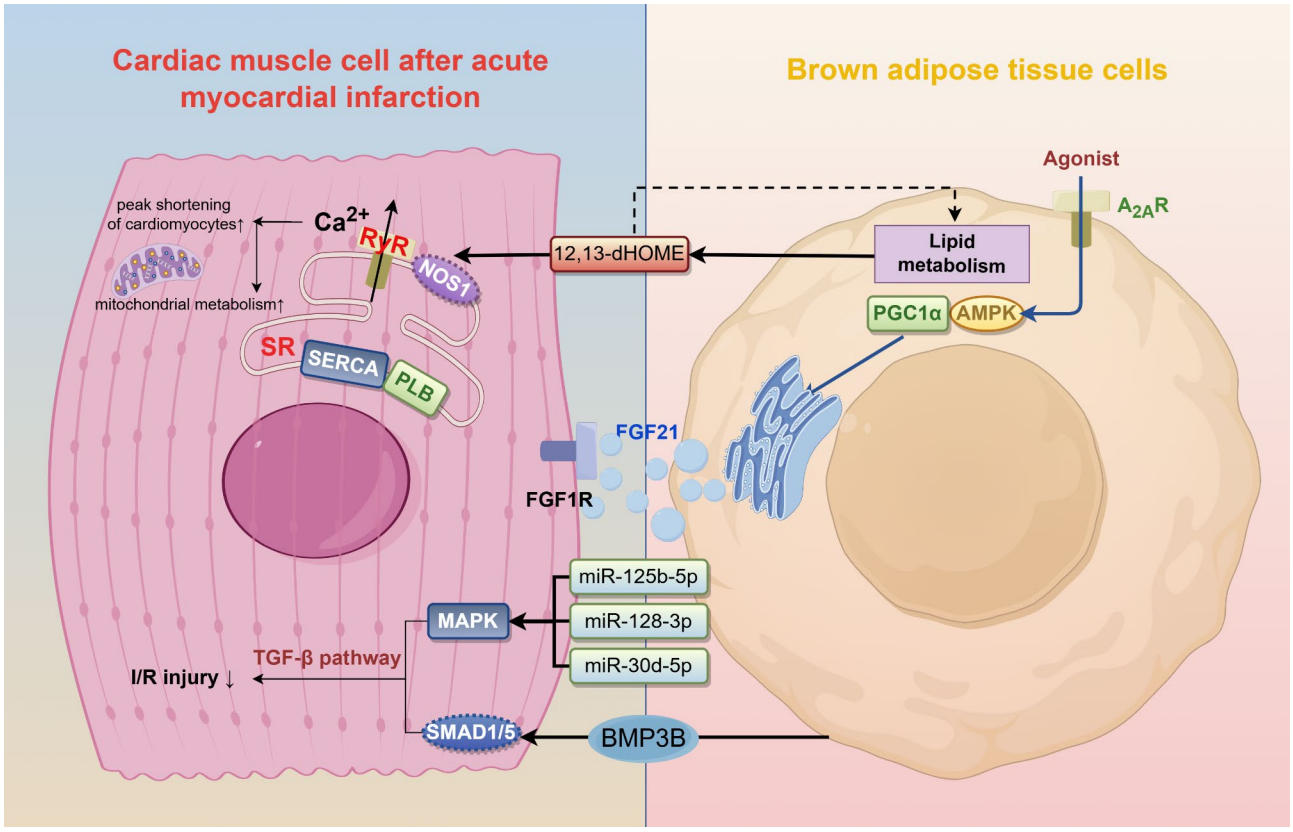

Fig. 1 The protective effect of brown adipose tissue on cardiomyocytes after myocardial infarction: in I/R injury, BAT secretes BMP3B protein and miRNA to regulate the TGF-β pathway in cardiac muscle cells to exert myocardial protective effects; in myocardial remodeling, cardiac muscle cell could receiving the signal communication from batokines like 12,13 diHOME and FGF21. These Batokines all have been proven to be produced by BAT in animal models of chronic myocardial remodeling

that agonistic ADRB 3, enables the release of BAT-Exos, which contains an increase in inducible nitric oxide synthase (iNOS). Coculturing BAT-Exos with NMCMS significantly enhanced the cross-sectional area and hypertrophic gene expression. Therefore, BAT-Exos are mediated by ADRB3, which reduces cardiac hypertrophy [20]. In addition, direct injection of BAT-Exos reduced cardiomyocyte hypertrophy in high-fat diet (HFD) fed mice, which led to the myocardial remodeling. Echocardiography showed improved EF and fractional shortening (FS) in HFD-fed mice after BAT-Exos treatment, with normalization of the E'/A' ratio. BAT-Exo treatment significantly improves myocardial systolic and diastolic functional damage in HFD-fed mice by reducing cardiomyocyte hypertrophy. Enrichment analysis in BAT-Exos revealed that the mitochondrial components were significantly enriched. BAT-Exos may be involved in the metabolic pathways in the myocardium [23].

Under normal physiological conditions, cardiac muscle cells use fatty acid β-oxidation as the main energy supply method. After AMI, cardiac muscle cell metabolism is reprogrammed, and mitochondrial intake of fatty acids is insufficient. Moreover, the rate of myocardial anaerobic glycolysis is much lower than that of aerobic oxidation, and large amounts of ions and lactic acid accumulate in the microenvironment, leading to a homeostasis imbalance [24]. BAT releases 12,13-diHOME, an oxidized linoleic acid metabolite, to improve CM metabolism. Previous studies have suggested that 12,13-diHOME increases the uptake of fatty acids in skeletal muscles and BAT, reduces circulating triglycerides, and improves lipid metabolism and insulin resistance [25]. The phenomenon of 12,13-dihome promoting fatty acid absorption also occurs in cardiomyocytes. Measurements of cardiac function in patients with heart disease showed that EF and FS were positively correlated with the 12,13-dihome levels. Moreover, 12,13-dihome activates the ryanodine receptor RyR through NOS1 signalling and increases Ca^{2+} circulation in cardiomyocytes, leading to an increase in the peak shortening of cardiomyocytes and enhancement of mitochondrial metabolism. Therefore, 12,13-dihome improves energy metabolism in cardiomyocytes [18]. Other studies have shown that BAT is activated in mice after the knockout of upstream stimulatory factor 1, which guides triglycerides from circulation into BAT. The activation of BAT enhances plasma triglyceride

clearance, which is further reflected in diet-induced increased thermogenesis, upregulation of mitochondrial respiratory chain complexes, and increased energy metabolism [26].

Batokines secreted by BAT play a protective role in cardiac muscle cells during early inflammation and the compensatory proliferation of myocardial remodeling, and actively improve the metabolic pattern of cardiac muscle cells.

BAT and myocardial fibrosis

Myocardial fibrosis is the main pathological process underlying AMI. The ischemic and necrotic myocardial cells were replaced with fibrotic cells. Simultaneously, fibroblasts and myofibroblasts were activated [27]. Myocardial fibrosis leads to reduced left ventricular compliance, and perivascular fibrosis hinders coronary recanalization [28]. BAT plays a myocardial protective role by limiting the progression of myocardial fibrosis (Fig. 2). Loss of BAT often causes the upregulation of the fibrosis genes Col1a1, TGFb and aSMA in mouse cardiac fibroblasts (CFs) [19]. Moreover, the extent of cardiac fibrosis was significantly aggravated in BAT-deficient mice [29, 30].

Mechanistic studies have shown that the BAT-specific factor ADRB3 limits angiotensin II (Ang II)-induced myocardial fibrosis via its effects on exosomes. In a coculture of brown adipocytes and CFs, ADRB3-deficient brown adipocytes elevated the levels of fibrosis genes α-SMA, Col1a1, and TGFβ in Ang II-stimulated CFs, significantly promoting CF proliferation. ADRB3 agonist treatment significantly alleviated Ang II-induced fibrotic features and reduced the fibrotic area. The main components of the exosomes were detected, indicating iNOS as an important component of BAT-Exos. Therefore, ADRB3 mainly limited myocardial fibrosis by inhibiting iNOS in BAT-Exos [20]. BAT can promote FGF21 secretion through the A_{2A}R-AMPK-PGC1a axis [19], and FGF21 is crucial in mitigating myocardial fibrosis.

AMPK signaling mediated by the adenosine 2a receptor (A_{2A}R) can promote the expression of the transcription factor PGC1a, thereby inducing the expression of FGF21

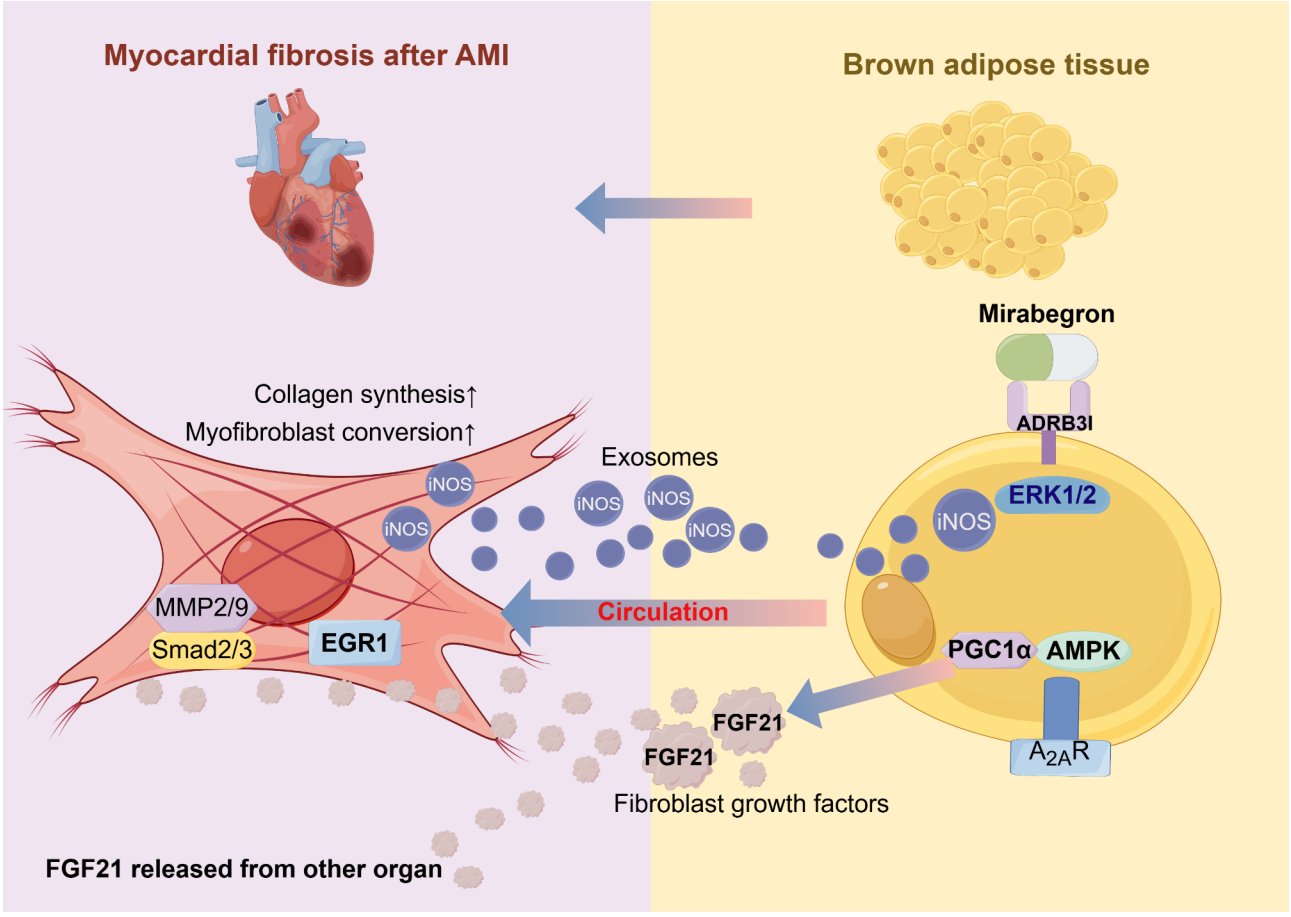

Fig. 2 Brown adipose tissue reduced fibroblast fibrosis after myocardial infarction: In the progression of myocardial fibrosis, ADRB3 was activated in BAT, and released the BAT-Exos (iNOS is the important component) thoughout the ERK1/2 pathway; another batokines FGF21 can also inhibit the TGF-β1-Smad2/3-MMP2/9 signalling pathway to alleviate myocardial fibrosis

in BAT [19]. FGF21 is considered an important molecule for improving cardiac remodeling in patients with hypertension and can alleviate cardiac dysfunction caused by myocardial fibrosis [31]. FGF21 promotes the expression of early growth response protein 1 (EGR1), which is accompanied by the downregulation of the fibrosis genes TGFβ, COL1, and COL3 [32]. FGF21 can also inhibit the TGF-β1-Smad2/3-MMP2/9 signaling pathway, thereby alleviating myocardial fibrosis [33]. However, the sources of FGF21 in the body are diverse and include BAT secretion, exercise, liver secretion, and cardiac autocrine signaling. Therefore, whether FGF21, specifically secreted by BAT, improves myocardial fibrosis after AMI requires further investigation.

BAT and HF

HF is a leading cause of mortality in patients after AMI [27]. In patients with severe HF, hypothermia is related to a poor prognosis, and BAT, which is related to thermogenesis, is activated. Tahara et al. reported two FDG-PET results from patients with non-ischemic dilated cardiomyopathy and a history of decompensated HF showed a significantly activation of BAT. Therefore, BAT activation is considered a new biomarker of severe HF. The activation of BAT may be caused by an increasing sympathetic nervous activity in patients with severe HF [34]. Another study found that BAT activation is associated with the nuclear tractus solitaries (NTS) [22], which is significantly expressed in the unmedullated vagal afferent nerve. In NTS, when the crucial channel transient receptor potential vanilloid 1 is inhibited, the sympathetic nerve activity of BAT, blood pressure, together with heart rate are altered. Therefore, sympathetic activation causes adipose tissue to exert improved metabolic effects [35]. However, the specific mechanism through which how sympathetic activation regulates BAT after AMI or HF remains unclear. Furthermore, in mice model of HF caused by the ligation of the left coronary artery for six weeks, magnetic resonance imaging revealed that although BAT was chronically activated, UCP1 mRNA levels increased. The stored lipids and BAT volume are in a state of consumption and gradually decrease [36]. Similarly, in rat model with salt-sensitive hypertension-induced HF, activated PKA-p38MAPK signaling was accompanied by increased levels of BAT-specific factors such as PPAR-γ, UCP1, and PGC-1α. At this time, BAT absorbs various FFAs. The levels of the transport proteins CPT-1, FATP-1, and CD36 were also increased. Overall, the heat production of BAT increased significantly in the HF model [37].

Notably, another study revealed that in HF with preserved ejection fraction (HFpEF), BAT mass was significantly increased; however, the levels of the BAT-specific genes UCP1, Cidea, and EVA were significantly decreased. The levels of lipolytic hormone-sensitive lipase, lipoprotein lipase, and fatty acid-binding protein 4, the major metabolic enzymes in BAT, were significantly reduced in HFpEF mice, and the physiological function of BAT was low. In addition, in HFpEF, MAPK phosphorylation of p38MAPK in WAT causes "adipose browning" and promotes its transformation into beige adipose tissue with a BAT phenotype [38]. Therefore, there are different results on the volume of BAT and the expression of UCP1 in different heart failure studies, showing all the possible causes related to the research on BAT in HF. First, this contradiction may be related to research detection time. In severe HF, BAT is consumed, and its myocardial protection is exhausted; therefore, the amount of BAT is reduced. Second, possibly related to the model chosen, HFpEF mice showed a significant increase in BAT quality, with significantly reduced expression levels of the BAT-specific genes UCP1, Cidea, and EVA. The conflicting outcomes might be attributed to the distinct myocardial protective mechanisms inherent to HFpEF. Finally, the results of the last few studies may have been related to the conditions of the selected patients. Tahara et al. reported the FDG-PET results of two patients in their study, and the observed BAT depletion in patients with HF may have been caused by patient bias. Overall, the BAT was activated in the HF group. Moreover, in an HF model induced by transverse aortic constriction, norepinephrine levels in BAT increase, and chronic activation of this signal can induce BAT dysfunction [39]. Therefore, BAT activation is speculated to be followed by consumption and functional impairment during HF progression. The myocardial protective mechanism is known to delay HF progression by reducing circulating TMAO levels. Therefore, it can be concluded that BAT is activated during HF and plays a protective role.

Further studies revealed that BAT protects the myocardium during HF progression. Compared with control mice, BAT-defective mice in the HF group had lower body temperature, higher probability of death, and worse cardiac function. BAT-defective mice exhibited increased apoptotic cardiomyocytes and cardiac fibrosis. Mechanistic studies revealed that the concentration of phosphorylcholine in the peripheral blood decreased two weeks after TAC. Under normal conditions, choline is absorbed and metabolized by healthy BAT. When BAT is dysfunctional, choline is oxidized to choline and trimethylamine-N-oxide (TMAO). TMAO inhibits mitochondrial complex IV activity in cardiomyocytes, reduces cardiac ATP production, and promotes HF progression [39]. Therefore, activated BAT can delay HF progression by reducing circulating TMAO levels.

Cardiogenic cachexia is a serious condition associated with late-stage HF. The main characteristics of patients are that their weight drops rapidly by more than 5%,

and the levels of various blood biochemical indicators decrease. Fat consumption is another characteristic of cardiogenic cachexia. In HF accompanied by cardiogenic cachexia, the heat production by BAT is enhanced, the fatty acid β-oxidation and "adipose browning" of WAT are enhanced, and WAT transforms into a cell state with a molecular phenotype of BAT. Additionally, IL-6 and norepinephrine levels rose in adipose tissue. Finally, increased heat production in BAT aggravates lipid consumption and promotes the progression of cardiogenic cachexia [37].

Effects of BAT in the treatment of AMI and HF

Application of BAT transplantation for myocardial protection

BAT transplantation is widely used in animal experiments and can effectively ameliorate myocardial damage in transplanted mice. Transplantation of iBAT significantly reduced the increase in plasma cardiac troponin I levels caused by ISO infusion [12]. Transplantation of iBAT during I/R significantly improved cardiomyocyte hypertrophy and reduced plasma cTnI levels [11]. Additionally, BAT improves insulin resistance, glucose tolerance, and obesity under physiological conditions [37]. BAT transplantation can also improve induced glucose intolerance and reduce exercise tolerance after AMI. The left ventricular mass of mice after AMI decreased after BAT transplantation, and exercise tolerance and glucose tolerance were preserved. Multiple peripheral tissue genes, including perigonadal WAT (pgWAT), subcutaneous WAT (scWAT), and liver genes, that affect glucose tolerance, were altered during AMI, and this expression was improved after BAT transplantation [40].

The results of animal BAT transplantation revealed that if the expected vascularization and innervation of transplanted BAT are similar to those of endogenous adipose tissue, it is necessary to make sure whether the transplanted BAT tissue contains platelet endothelial cell adhesion molecule 1, so that the expected vascularization of the transplanted BAT could be determined. Also, the tyrosine hydroxylase expression is used to determine expected innervation [11]. This can provide a research basis for the further exploration of BAT in human transplantation.

Application of BAT agonists and batokines for myocardial protection

Based on previous studies, myocardial protection can be achieved using either BAT agonists or batokine analogs. BAT is most prominently characterized as a thermogenic fat that is activated under cold conditions. In addition, β-AR agonists [41], glucagon-like peptide 1 receptors [42], and FGF21 [43] can directly act on BAT.

Batokines can be used to develop BAT adipokine analogs. The batokine FGF21 secreted by BAT acts directly on cardiomyocytes. Also, the FGF21 receptor (FGFR1) is significantly expressed in cardiomyocytes, together with the high-expressed of its coreceptor (β-Klotho). FGF21 induces FGFR1-mediated phosphorylation of extracellular signal-regulated kinase 1/2 [22]. In addition to FGF21, there are also batokines such as IL-6 [44], 12,13-diHOME [18], BMP3b [11], and BAT-Exos [20] that have protective effects on cardiomyocytes. However, the origin of these molecules is often not limited to BAT. For instance, IL-6 is produced in cardiac, smooth and skeletal muscles [44]; thus, the specific cardioprotective function of BAT-derived adipokines requires further validation. In addition, the damage caused by BAT adipokines to other target organs, and the effect of increased thermogenesis caused by activated BAT on the post-AMI period require further investigated.

BAT can be used as an adjuvant therapy to promote treatment effectiveness after AMI. Exercise is considered a meaningful treatment after AMI and can reduce CVD-related all-cause mortality [45]. Moreover, exercise can make WAT decreased and BAT increased to reshape the composition of the adipose tissue [46, 47]. Small extracellular vesicles, which secreted by BAT and carrying the miRNAs in, directly mediate the exercise protective effects against I/R injury. Therefore, while performing exercise therapy, activating BAT to increase miRNA levels and the myocardial protective effects of exercise are considered potential improvements strategies [14].

Application of brown adipose tissue stem cells (BADSCs) for myocardial protection

BADSCs are also found in BAT and are considered to have the potential to differentiate into cardiac muscle cells. Among them, CD29-positive BADSCs have the greatest cardiac muscle cell differentiation ability. Implanting CD29 BADSCs into the infarcted region replaces the generation of new cardiac muscle cells, reduces the infarct area, and improves left ventricular function [48–50]. Therefore, BADSCs are often combined with various biological materials for post-AMI treatment, the most important of which are hydrogels [51, 52] and biological patches [53]. The newly developed Zwitterionic starch-based hydrogel can provide a suitable microenvironment for BADSCs to maintain their "stemness" while maintaining stable cardiomyocyte differentiation and expansion [54]. The biopatch was mainly composed of BADSCs stacked layer by layer and can accelerate angiogenesis and reduce cardiac inflammation, ultimately activating the renewal of cardiac muscle cells [53].

Other applications of BAT in the cardiovascular system

BAT promotes the consumption of fatty acids and aggravates cardiac cachexia. Therefore, the inhibition of BAT thermogenesis is considered a feasible treatment. APS is an important active component isolated from Astragalus membranaceus. It inhibits enhanced heat production in BAT in cardiogenic cachexia. Experiments have shown that high-dose APS treatment inhibits, the PKA-p38 MAPK pathway in BAT. Additionally, thermogenic genes expression such as UCP1, PGC-1α and PPAR-γ were inhibited, while IL-6 and NE mRNA levels in BAT were upregulated. After APS treatment, the EF and FS of the patients rebounded, and cardiac function improved. Therefore, APS delays lipid consumption and improves cardiogenic cachexia by inhibiting heat production and inflammation in BAT [37].

Conclusion and future directions

As a unique type of adipose tissue, BAT participates in multiple metabolic pathways, such as lipid and energy metabolism. In AMI, HF, and related diseases, BAT plays myocardial protective roles through signal exchange with cardiac muscle cells and fibroblasts. During I/R, BAT produces brown adipokines such as BMP3B protein and miRNA through its endocrine function to ameliorate myocardial injury, reduce the infarct scope, and play a myocardial protective role. The next chronic change that occurs after I/R is myocardial remodeling. BAT is considered an important regulatory molecule in the pathological process of myocardial remodeling, and ultimately plays a protective role in cardiac cells by regulating early inflammation, compensatory hypertrophy and metabolic reprogramming. Myocardial fibrosis is a long-term process, in which BAT mainly regulates fibroblasts by secreting batokines to slow down myocardial fibrosis progression. HF is often a long-term outcome in patients with AMI, and BAT is activated in clinical patients. The mechanism underlying myocardial protection by BAT in HF is the delay of the process involved in HF by reducing circulating TMAO.

In addition, there are some well-studied adipokines such as Nrg4 [55] and 12,13 diHOME [18], which are still lacking detailed reports on whether they are activated after AMI and whether they play a myocardial protective role. Therefore, it is necessary to explore the additional function of brown adipokines in AMI associated with cardiomyocytes or fibroblasts, thereby playing a myocardial protective role. In HF, studies on BAT and the heart have primarily focused on phenotypic research. Hoping further researches will elucidate the mechanism underlying myocardial protection of BAT in HF.

The multiple endocrine function of BAT is to safeguard cardiac cells, mainly by regulating the AMI and HF processes. BAT transplantation and the application of batokines are considered effective treatments. However, the rejection of allogeneic BAT transplantation and the diversity of sources and target organs of batokines are problems that need to be addressed in BAT treatment. Therefore, further research on improved transplantation of BAT and the development of drugs targeting cardiac cells with specific batokines is needed. Once BAT transplantation and drug-mediated BAT activation can be applied clinically, all of these will benefit future treatments for patients with AMI, HF, and associated cardiovascular diseases.

Abbreviations

18F-FDG	18 F-fluorodeoxyglucose
ADRB3	adrenoceptor Beta 3
AMI	acute myocardial infarction
AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
AngII	angiotensin II
$A_{2A}R$	adenosine 2a receptor
ATP	adenosine triphosphate
BAT	brown adipose tissue
Batokines	brown adipose tissue adipokine
BADSC	brown adipose tissue stem cells
BMP3b	bone morphogenetic protein 3b
CFs	cardiac fibroblasts
CT	computed tomography
CVD	cardiovascular disease
EF	ejection fractions
EGR1	early growth response protein 1
ESV	end-systolic volume
FGFR1	fibroblast growth factor 21 receptor
FGF21	fibroblast growth factor 21
FS	fractional shortening
HF	heart failure
HFD	high-fat diet
HFpEF	heart failure with preserved ejection fraction
I/R	ischemia/reperfusion
IL	interleukin
iNOS	inducible nitric oxide synthase
iBAT	active brown adipose tissue
MAPK	mitogen-activated protein kinase
NMCMs	neonatal mouse cardiomyocytes
NTS	nucleus tractus solitaries
PET	positron emission tomography
sEVs	small extracellular vesicles
TAC	transverse aortic constriction
TGF	transforming growth factor
TMAO	choline and trimethylamine-N-oxide
UCP1	uncoupling protein 1
USF1	upstream stimulatory factor 1
WAT	white adipose tissue

Acknowledgements

Figures were created by Figdraw, and the manuscript get language editing from curie and editage.

Author contributions

ZX drafted the main text and generated the graphical illustrations. HL participated in drawing the table, GJC, PPL and HTZ participated in revising the image. YS revised and edited the manuscript. All the authors have read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (grants no. 82270286, 82170336, and 81870266).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 3 July 2024 / Accepted: 6 October 2024
Published online: 16 October 2024

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